REMARKS

FORMAL MATTERS

Claims 22 to 25 have been added.

Support for claim 22 can be found in claim 8 as originally filed and throughout the specification (see, e.g., Example 7 beginning on page 34 of the specification).

Support for claim 23 can be found in the specification in Example 3, beginning on page 28; Example 7, starting on page 34 (see paragraph spanning page 35 and 36); Example 8A, beginning on page 36; Example 8C, beginning on page 40; and Example 9, beginning on page 43.

Support for claim 24 can be found in the specification in the abstract and on page 20 under the heading "F. Pharmaceutical Compositions".

Support for claim 25 can be found in the specification in Example 4, starting on page 29, and Example 11, starting on page 47.

No new matter is added by way of these amendments.

REJECTIONS UNDER §101 AND §112, ¶ 1

Claims 1-3, 8-10, 20 and 21 were again rejected under 35 U.S.C. §101 as allegedly not supported by either a specific and substantial asserted utility or a well-established utility. Applicants respectfully disagree.

In maintaining this rejection, the Examiner states that:

> The utility analysis for the claimed method is based upon the utility of the agonists and antagonists screened by the method. Since neither the prior art nor the specification discloses the biological functions or physiological significance of the orphan G protein coupled receptors, the agonists and antagonists do not have a specific and substantial utility. (see pages 3 and 4 of the Office Action).

Applicants respectfully submit that, contrary to the Examiner's assertion above, both the art and the specification disclose the biological function or physiological significance of specific orphan GPCRs.

As a first example, the specification shows that the expression of the orphan receptor GPR3 is higher in brain biopsy tissue (temporal cortex) from subjects suffering from epilepsy as compared with

control tissue (see Example 7 and Figure 8). This disease-specific expression pattern provides the impetus for screening for candidate agonist/inverse agonist compounds of GPR3.

In addition, Examples 8 and 9 in the specification provide a series of experimental results that implicate GPR6 as playing a role in feeding regulation. Specifically, Examples 8A shows that GPR6 is expressed in the hypothalamus, hippocampus, nucleus accumbens, caudate and cerebral cortex of rat brain (see Figure 9A and B). This Example goes on to compare GPR6 expression levels between lean and obese male Zucker rats (Charles River). The results in Figure 10 show that the endogenous, constitutively activated orphan receptor GPR6 is relatively over-expressed in this model of obesity (i.e., expression is higher in the obese Zucker rats), indicating that GPR6 may play a role in feeding regulation. Supporting these results, Applicants go on to demonstrate that reducing the expression of GPR6 in vivo in rats (using anti-sense oligonucleotide technology to "knock down" GPR6 expression in the brain) results in significantly greater loss of weight as compared with either the missense oligonucleotide-treated animals, or the control-treated animals (see Figures 15 and 16).

Following up on these findings regarding the GPR3 and GPR6 orphan receptors, Example 11 in the specification describes the identification of an inverse agonist of GPR3 and both an inverse agonist and an agonist of GPR6 according to the claimed invention (see Figures 17A and B).

Because the specification provides a clear example of the utility of the claimed invention, i.e., screening candidate compounds for agonist/inverse agonist activity for an orphan GPCR of interest, Applicants submit that the subject claims satisfy the requirements under 35 U.S.C. §101. For this reason alone this rejection may be withdrawn.

In addition to the support for the utility of the claimed invention in the specification, Applicants submit that examples of orphan GPCRs with known functional activity have been described in the art, including orphan GPCRs for which pharmaceutical agents have been developed and marketed without any understanding of their natural ligand.

First, Applicants have previously submitted to the Examiner references demonstrating that the orphan receptors STRL33, gpr1 and gpr15 act as co-factors for retroviral entry into cells: (i) Liao et al.,

The Journal of Experimental Medicine (June 2, 1997) vol. 185, p. 2015-2023, entitled "STRL33, A Novel Chemokine Receptor–like Protein, Functions as a Fusion Cofactor for Both Macrophage-tropic and T Cell Line–tropic HIV-1"; (ii) Alkhatib et al., *Nature* (July 17, 1997) vol. 388, p. 238, entitled "A new SIV co-receptor, STRL33"; and (iii) Farzan et al., *The Journal of Experimental Medicine* (August 4, 1997) vol. 186, p. 405-411, entitled " Two Orphan Seven-Transmembrane Segment Receptors Which Are Expressed in CD4-positive Cells Support Simian Immunodeficiency Virus Infection". These references clearly establish that an orphan GPCR can be associated with a function or activity (e.g., viral entry into a cell).

Therefore, in view of the teachings of both the specification and the art, Applicants submit that the claimed invention is supported by both a specific and substantial asserted utility and a well-established utility. In sum, Applicants submit that identifying modulatory compounds for such functionally-characterized orphan GPCRs represents a specific, substantial "real world" use of the claimed invention.

The description above is provided merely to establish that, contrary to the assertions in the Office Action, orphan GPCRs having known functional activities were known at the time of filing the instant application, thus establishing a specific and substantial "real world" utility of the claimed invention. However, Applicants stress that it is *the user of the claimed methods* who determines which orphan GPCR to employ based on their own criteria, not on any pre-conceived criteria supplied by Applicants and/or the art. As such, the description of the orphan GPCRs above is not meant in any way to limit the scope of the claimed invention in this regard.

Applicants further submit that a person skilled in the art would not make the effort to screen an orphan GPCR if they did not have some reason to do so (i.e., a use for the compounds identified by the screening method). In other words, the claimed screening assay has a specific and substantial "real world" use because it allows a user to identify, from a library of candidates, specific compounds that have a defined modulatory activity for an orphan GPCR of interest to them, regardless of the reason.

With regard to Applicant's prior arguments that the utility of the claimed invention was analogous to the utility of the polymerase chain reaction (PCR), the Examiner replied that "unlike PCR

technology, the instant claims are drawn to "a method of screening", not a tool for studying and monitoring any particular diseases."

Applicants agree that the instant claims are drawn to a method of screening, but do not consider this to detract from the argument that the utility of the claimed invention is analogous to the utility of PCR.

As argued previously, Applicants contend that the utility of PCR is derived from its ability to amplify virtually any polynucleotide sequence that is of interest to a user, regardless of its specific sequence, function or association with a disease or condition. Likewise, the utility of the claimed invention is derived not from the specific identity of the GPCR employed in the method, but rather from the ability of one to use the claimed methods to identify modulating compounds for virtually any orphan GPCR that is of interest to them. Specifically, a user of the claimed invention of the instant application has in hand an orphan GPCR for which candidate agonist/inverse agonist compounds are sought. Thus, similar to the fact that the utility of PCR is not tied to a specific polynucleotide sequence of interest (i.e., a sequence to be amplified), the utility of the subject invention is not tied to a specific orphan GPCR to be screened.

As established above and in prior responses, Applicants submit that there existed, at the time the application was filed, orphan GPCRs with known functional properties and that identifying modulatory compounds for such functionally-characterized orphan GPCRs represents a specific, substantial "real world" use of the claimed invention. The fact of the existence of orphan GPCRs having no known function does no more to negatively impact the real world utility of the claimed invention than does the the existence of nucleic acid sequences having no known function negatively impact the real world utility of PCR. Indeed, even though at the time PCR was invented there were vast amounts of nucleic acid sequences in the human genome (and elsewhere) with no known function, the utility of the PCR method was clear.

In this context, Applicants bring to the attention of the Examiner an example from the GPCR screening field of patented claims that are not limited to a particular GPCR: U.S. Patent No. 5,462,856 (a copy of which is provided with this Amendment). The '856 patent, entitled "Methods for identifying

chemicals that act as agonists or antagonists for receptors and other proteins involved in signal transduction via pathways that utilize G-proteins," claims an assay in which the aggregation or dispersion of pigment in melanophore cells is used as a read-out for whether a candidate compound is an agonist or antagonist of a GPCR. Importantly, none of the issued claims are limited to a particular GPCR, as knowledge of the sequence or function of the screened GPCR is not necessary to the screening method. The claims have a real world utility because they allow a user to screen for agonist/antagonist compounds specific for a GPCR of interest to them, similar to the claims of the subject application.

Applicants submit that the claims of the subject application generally are directed to methods used in a research setting which plays an important role in developing a biopharmaceutical end product (compounds), where without it, the end product would either not have been found or found only after a great deal of effort and expense. Specifically, as discussed in the specification and in previous responses, modulatory compound screens for orphan receptors were not carried out until they had been "de-orphanized" (i.e., an endogenous ligand had been identified). However, finding an endogenous ligand for an orphan receptor was, and still is, very expensive, time consuming and oftentimes unsuccessful. The claimed methods provide way to screen for compounds that modulate an orphan receptor's activity without first de-orphanizing the receptor (i.e., identifying the endogenous ligand).

With regard to the utility of research tools, MPEP 2107.01(C) states the following:

> C. Research Tools
> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

As stated above, inventions that are used in a research or laboratory setting, including screening assays as claimed in the present invention, have "a clear, specific and unquestionable utility" provided they have a "specifically identified substantial utility". In the case of the subject invention, the screening assay method identifies compounds that have modulatory activity on an orphan GPCR of interest to a user. Such functionally characterized compounds can be employed in a predictable manner as reagents that have a known effect on the orphan GPCR (i.e., as agonists or inverse agonists). Coupled with the fact that orphan GPCRs had been, and still are being, associated with specific functions, diseases or disorders, the claimed invention has a clear, specific and unquestionable utility in a patent sense.

In view of the arguments above, the Applicants submit that the claimed invention meets the requirements under 35 U.S.C. §101 and thus respectfully request that this rejection be withdrawn. Furthermore, because the claimed invention was rejected under 35 U.S.C. §112, 1st paragraph solely for allegedly not meeting the requirements under 35 U.S.C. §101, Applicants also respectfully request that the §112, 1st paragraph rejection be withdrawn.

REJECTIONS UNDER §103(a)

Claims 1-3, 8-10, 20 and 21 were again rejected under 35 U.S.C. § 103(a) as allegedly obvious over Seifert et al. (J. Biol. Chem. 1998, Vol. 273, No. 9, 5109-51 16) in view of Scheer et al. (J. of Receptor and Signal Transduction Research, 1997, Vol. 17, 57-73) and further in view of Song et al. (Genomics, 1996, Vol. 28, 347-9), Bertin et al. (PNAS USA, 1994, Vol. 91, 8827-8831) and Wise et al. (J. Biol. Chem., 1997, Vol. 272, No. 39, 24673- 24678). Applicants respectfully traverse this rejection.

The Applicants again note that the present §103 rejection is nearly identical to the §103 rejection presented by the Examiner in the previous Office Action. The claims and the arguments employed to rebut this rejection mirrored those made during prosecution of the 6,653,086 patent (which were sufficient to overcome the rejection). However, the Examiner has failed to provide any further clarification of why the amendments and arguments are now considered non-persuasive. Without such clarification, Applicants have no guidance as to why the Examiner has maintained this rejection.

Therefore, the arguments presented below are largely duplicative of the previous arguments. Applicants respectfully request that the Examiner reconsider these arguments and, if again found unpersuasive, please provide the Applicants with comments directed to why the specific amendments and arguments, which were persuasive in the parent case, are now insufficient to overcome this rejection.

Deficiencies in Seifert, Scheer, Bertin, and Wise

Seifert is drawn to "Different Effects of Gsα Splice Variants on β2-Adrenoreceptor-mediated Signaling", and discusses the generation and testing of the β2-Adrenoreceptor coupled to splice variants of Gsα. The β2-Adrenoreceptor, although a G Protein Coupled-Receptor, is not an orphan G protein coupled cell surface receptor. Indeed, the endogenous ligand for the β2-Adrenoreceptor is known and the receptor has been characterized. As acknowledged by the Examiner, Seifert fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Also acknowledged by the Examiner is the fact that Seifert fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

In addition, Applicants emphasize that Siefert fails to teach identifying compounds as agonists or inverse agonists as claimed. Rather, Siefert employs known agonists and inverse agonists of the GPCR under study as a way to study differences in signaling from the different forms of the β2-Adrenoreceptor. In other words, Siefert does not teach or suggest a compound identification assay as claimed.

In keeping with this deficiency in Siefert, this reference also fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, the Scheer reference discusses "[t]he activation process of the α_{1B}-adrenergic receptor: Potential role of protonation and hydrophobicity of a highly conserved aspartate." However, ligands for the β2-Adrenoreceptor are known (see, for example, Table 1 of Scheer which

discusses ligand binding properties of the adrenergic receptor), and the receptor has been characterized. Scheer fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Scheer also fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

Finally, Scheer fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, Bertin discusses the "[C]ellular signaling by an agonist-activated receptor/Gsα fusion protein", and discusses fusions of the β2-Adrenoreceptor/Gsα. As discussed in relation to the Seifert and Scheer references, ligands for the β2-Adrenoreceptor are known (see, page 8828 of Bertin which discusses the use of ICYP as a ligand), and the receptor has been characterized (see Table 1 and Figure 3 which set forth pharmacological properties of the receptor). Bertin fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

In addition, Bertin also fails to teach or even disclose the particular G protein coupled receptor for which the endogenous ligand has not been identified -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

Finally, Bertin also fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, the Wise reference discusses the "[R]ole of Functional Interactions between the α_{2a} -Adrenoreceptor and Acylation-resistant Forms of $G_{i1\alpha}$ by Expressing the Proteins from chimeric Open Reading Frames", and discusses fusions of α_{2a}-Adrenoreceptor and $G_{i1\alpha}$. However, ligands for the α_{2a} -Adrenoreceptor are known (see, page 24674 of Wise which discusses the use of RS-79948-197 as a ligand), and the α_{2a} -Adrenoreceptor has been characterized. Wise fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Further, Wise also fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR2 1, OGRI, GHSR, RE2 and AL022171.

Finally, Wise fails to teach or suggest the final candidate identification step recited in the claims as amended.

Therefore, the combined teachings of Seifert, Scheer, Bertin, and Wise fail to teach or even suggest at least the following: 1) a method for directly identifying a non-endogenous candidate compound as an inverse agonist or an agonist, to an endogenous, constitutively active orphan GPCR, 2) particular orphan G protein coupled receptors (e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171), and 3) the final candidate identification step recited in the claims as amended.

Song fails to Remedy the Deficiencies in Seifert, Scheer, Bertin, and Wise

The Song reference fails to remedy the deficiencies of Seifert, Scheer, Bertin and Wise, alone or taken in combination. Song fails to teach or even suggest a method for directly identifying a non-endogenous candidate compound as an inverse agonist or an agonist, to an endogenous, constitutively active orphan G protein coupled cell surface receptor. As its title indicates, the Song reference discusses the "Molecular Cloning and Chromosomal Localization of Human Genes Encoding Three Closely Related G Protein-Coupled Receptors", one of which is GPR6, an orphan GPCR.

However, Song fails to teach or suggest any method for identifying agonists or inverse agonists of a GPCR, less still a method for identifying agonists or inverse agonists of a constitutively active orphan GPCR.

In addition, Song also fails to teach or suggest the final candidate identification step recited in the claims as amended.

Therefore, the applicants submit that the combined teachings of the cited references fail to teach or suggest each and every limitation of the claimed invention.

The Examiner also asserts that one would be motivated to modify the teachings of Seifert, Scheer, Bertin and Wise with the teaching of Song (described by the Examiner as a constitutively active GPCR), to allegedly achieve Applicants' claimed invention, citing several passages from the cited references as alleged motivation for modifying the teachings of the same.

However, none of the cited passages contains any disclosure or suggestion whatsoever to apply the disclosure of methods relating to GPCRs with known ligands to orphan GPCRs. Indeed, none of the quotations provided by the Examiner refer to orphan receptors at all, and Applicants are unable to locate any reference to orphan receptors in any of Seifert, Scheer, Bertin and Wise.

Further, the Song reference fails to teach or suggest any method for identifying agonists or inverse agonists of a GPCR. Thus, in addition to a lack of legally sufficient reason to combine the teachings of the cited art, even when so combined the combination would not teach Applicants' invention as presently claimed. Prior to Applicants' invention, there was no teaching in the art that constitutively active orphan G Protein-Coupled Receptors were useful for determining agonists and inverse agonists of the receptor. Rather, prior research involving orphan GPCRs was focused on identifying the ligand of the receptor, often using homology to receptors with known ligands as a guide. The prevailing wisdom in the GPCR field was that the determination of agonists or antagonists of a GPCR was an activity that invariably happened after the ligand was identified.

Accordingly, the skilled artisan had no reason to combine the teachings of Seifert, Scheer, Bertin and Wise with the teachings of Song. Indeed, the only source of such motivation is Applicants' own disclosure, and, as has been invariably held by the Courts, the use of an Applicant's specification as reason to combine or modify references in an obviousness analysis is not permissible.

In view of the discussion above, it is clear that the Examiner has failed to establish a *prima facie* case of obviousness for the claimed invention. Indeed, this same rejection was successfully traversed by the Applicants in the '086 patent, which claims similar subject matter.

Therefore, because the Examiner has failed to provide a legally sufficient reason to combine the teachings of references as asserted in the Office Action, and because such combination would not result in Applicants' claimed invention, Applicants respectfully request withdrawal of this rejection.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-3, 10 and 20 have been rejected on the ground of non-statutory obviousness type double patenting as being unpatentable over the claims of U.S. Patent 6,653,086.

Applicants respectfully request that this rejection be held in abeyance until patentable subject matter is identified in the subject application.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-005CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 11, 2010

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